Livedoid Thrombotic Vasculopathy Responding to Doxycycline Therapy

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ABSTRACT

Livedoid vasculopathy is a disease of the lower extremities that occurs predominantly in women. It begins as purpura and eventually ulcerates. Multiple causes have been posited, but many cases are found to be idiopathic. Many treatment modalities have been attempted to control the disease process, but many cases remain difficult to treat, and, at times, the treatments have side effects that limit treatment. This is a case report in a small number of patients tested in unblinded fashion. We report the effective use of doxycycline in the treatment of long-standing livedoid vasculopathy in two patients. (*J Clin Aesthetic Derm.* 2008;1(4):22–24.)

Livedoid vasculopathy was initially described in 1967 by Bard and Winkelman.[1] It was originally called *atrophie blanche en plaque* by Milian in 1929.[2] The disease has been called many names including livedo reticularis with ulceration, livedo vasculitis, livedoid vasculitis, and segmental hyalinizing vasculitis.[3]

Livedoid vasculopathy is characterized by focal areas of purpura on the leg that ulcerate and progress to atrophic stellate scarring. These ulcerations are typically painful and often have evidence of thrombosis. Histology typically shows hyalinizing vascular change of the intimal vessels with minimal inflammation. Livedoid vasculopathy has been reported to have multiple etiologies including elevated fibrinopeptide A,[4] antithrombin III deficiency,[5] dermal vascular occlusion,[6] immune complex disease,[7] increased release of plasminogen activator,[8] and idiopathic.[9]

Multiple treatments have been proposed, including low-dose aspirin,[10] dipyridamole,[10] warfarin,[11] hyperbaric oxygen,[12] pentoxyphylline,[13] and intraveneous immunoglobulin.[14] In 2006, Callen et al gave a diagnostic workup and treatment ladder for therapy of livedo reticularis.[15]

We report two cases of long-standing livedoid vasculopathy that responded to doxycycline therapy and recurred upon cessation of treatment.

CASE 1

A 52-year-old man with controlled hypertension presented with a 25-year history of painful lower extremity ulceration that had failed to heal in an ulcer clinic (Figure 1). The patient denied a history of trauma or deep vein thrombosis. He complained of lower-extremity edema and significant pain associated with the ulcerations. Biopsies were performed. One biopsy revealed a thrombotic vasculopathy without periodic acid Schiff (PAS) staining of the intravascular sludge (Figure 2). A second biopsy revealed changes consistent with stasis change and fibrosis.

Free protein S was found to be elevated at 142 percent (normal 64–125%). Lupus anticoagulant, anticardiolipin-antibody, homocysteine, antithrombin III, β2-glycoprotein, and functional protein C were within normal limits. The patient was deemed to have thrombotic vasculitis consistent with livedoid vasculopathy. Doxycycline therapy at 100mg twice daily was instituted with substantial improvement noted within two weeks and near complete healing within 2.5 months. The patient also reported alleviation of nearly all pain and edema with the healing of the ulcers.

Over the next three years, the ulcers have recurred upon cessation of doxycycline therapy and healed upon reinstitution of the medication.

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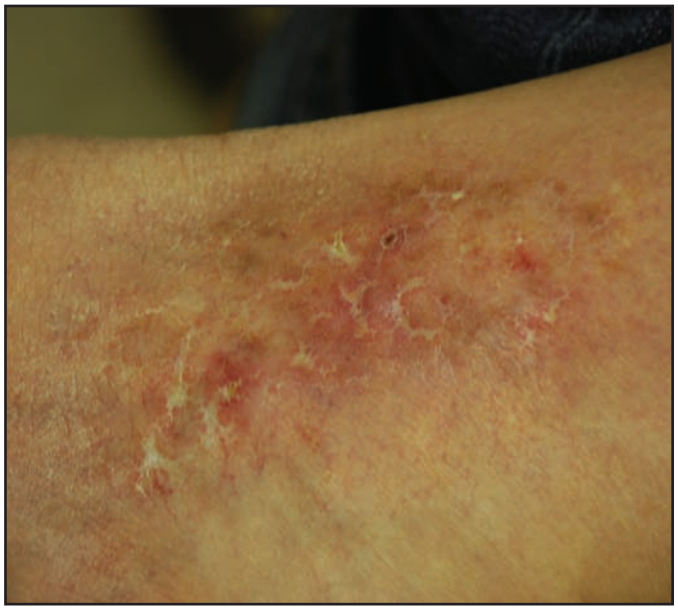

Figure 1. Stellate scarring and a nearly healed ulcer on the ankle of the patient described in Case 1.

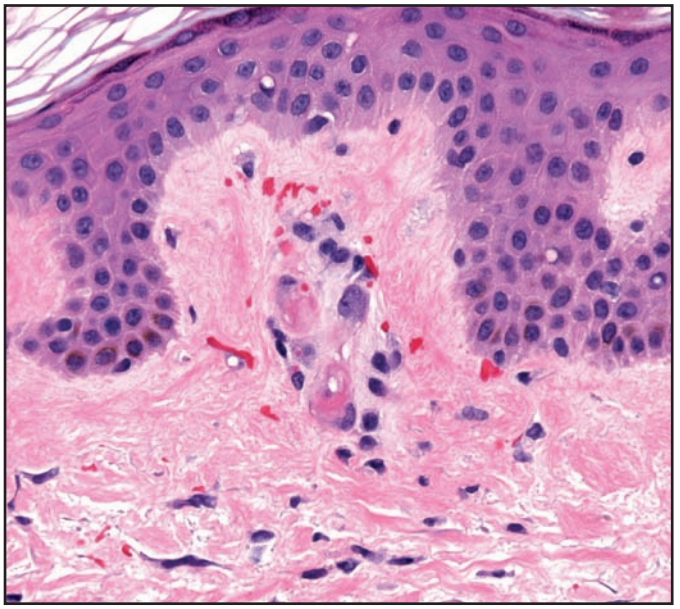

Figure 2. High-power view of upper leg biopsy; thrombosis and sludging of superficial vessels with extravasation of erythrocytes; PAS staining of the intracellular material was negative; 400x.

CASE 2

A 73-year-old woman with a history of chronic obstructive pulmonary disease (COPD) presented with an 11-year history of right lower extremity ulcers and edema (Figure 3). The cause of the ulcer was initially thought to be cryoglobulinemia, and the patient was treated with stanazol at an outside institution. The patient achieved no benefit while on the medication, which was discontinued due to side effects. A biopsy was performed by an outside institution, and the clinicopathologic correlation was believed to be consistent with livedoid vasculopathy. The patient was grafted at one time in an attempt to close the wound. Serum protein electrophoresis revealed only an elevated alpha-2 globulin, which was believed to be an acute phase reactant.

Physical examination revealed two painful ulcerations with associated atrophie-blanche-type scarring and moderate edema. Erythrocyte sedimentation rate was elevated slightly at 54mm/hr. The patient was mildly anemic with a hemoglobin of 11.5g/dL with a low iron and percent saturation, but a normal reticulocyte count.

Evaluation of thyroid-stimulating hormone, lupus anticoagulant, prothrombin time/partial thromboplastin time, aspartate aminotransferase/alanine aminotransferase, and cryoglobulins were within normal limits. There was no evidence of chronic hepatitis.

Doxycycline 100mg twice daily was instituted with improvement of ulcer size, lower-extremity edema, and pain within a month and nearly complete healing within a few months of therapy. The patient's ulcer was painless and nearly healed when she was instructed by another physician to discontinue doxycycline because of a pulmonary infection and COPD exacerbation. A rapid increase in size of the ulcer and increase in pain was noted upon discontinuation of doxycycline. Upon reinstitution of doxycycline therapy, improvement of the ulcer, edema, and pain was again noted.

DISCUSSION

Doxycycline is a second-generation tetracycline antibiotic with broad-spectrum antimicrobial activity.[16] Tetracyclines have anti-inflammatory properties that make them useful in the treatment of acute and chronic inflammatory conditions, such as periodontal, neurologic, and dermatologic diseases. Doxycycline has been shown to inhibit the acute immune response reducing cell migration, edema, neutrophil activity, fibrovascular tissue formation, and nociception. This activity is thought to derive from the ability of doxycycline to inhibit matrix metalloprotease activity, neutrophil chemotaxis, and production of nitric oxide, prostaglandin E2, interleukin-1β, interleukin-6, tumor necrosis factor-α, phospholipase A2, and protein kinase C.[17,18,19]

The mechanism by which doxycycline controls a fundamentally thrombotic process—livido vasculitis—is not obvious and deserves further attention. The two patients that we report had similar skin disease, but presumably different mechanisms by which it occurred, since only one had an identifiable hypercoagulable state. These patients were well controlled on a widely used medication after years of other failed treatments. Should doxycycline be considered for livido vasculitis therapy in future patients it is important to identify those who are at risk for thrombosis elsewhere due to underlying hypercoagulability and to treat that accordingly since there is no evidence (or reason to suspect) that doxycycline is protective against thrombosis in general.

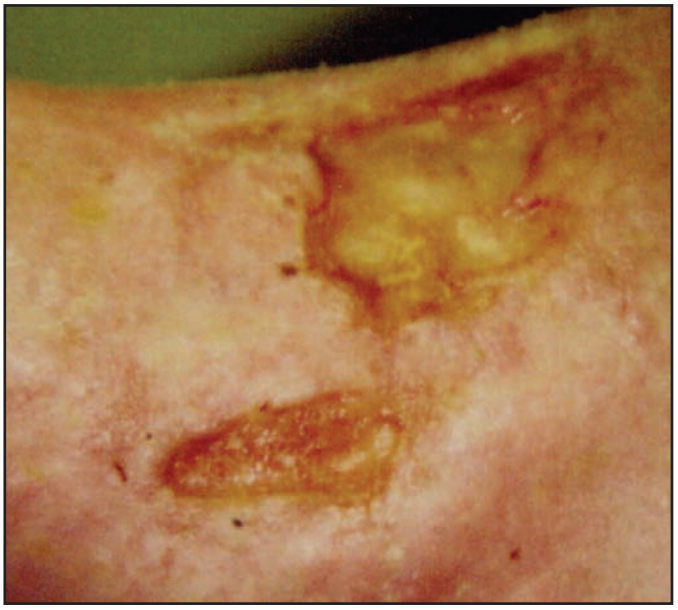

Figure 3. Stellate ulcers on the right medial ankle of the patient described in Case 2.

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